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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,940	SCHENK, DALE B.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-58* is/are pending in the application.

4a) Of the above claim(s) *38-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Response and Amendment filed 15 September 2003 has been received and entered in full. Claims 31-37 are under examination.

2. The Statement under MPEP §2406.02 filed 25 November 2003 has been received and taken into consideration.

3. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Election/Restrictions

4. Applicant's election with traverse of Group I (claims 31-37) drawn to in the Response and Amendment filed 15 September 2003 is acknowledged. The traversal is on the ground(s) that (a) Groups III which is drawn to a vaccine for preventing and/or treating an amyloid-related disease in a subject cannot be used to isolate receptors as put forth in the Restriction Requirement (), (b) Claims 32, 39, 46, and 53 are not generic. Claims 31, 38, 45, and 52 are generic because the cover all respective species and claims 32, 39, 46, and 53 are subgeneric relative to claims 32, 38, 45, and 52 because they cover some but not all of the respective species, and (c) Group II which is drawn to a vaccine for preventing and/or treating an amyloid-related disease can not be used in *in situ* and diagnostic assays. Thus the Applicant requests that Groups I and III be rejoined as well as Groups II and IV.

5. This is not found persuasive because in regards to (a) and (c), the recitation of a "vaccine" is an intended use term for a product claim. Therefore the preamble is given not patentable weight and the product is considered only on the merits of its material properties. As claimed, Group III's peptides can be used in biochemical assays including but not limited to isolating receptors. Said peptides can also be used in an *in vitro* cell death assay and the like. The same is true for the peptides of Group II. In regards to (b), the claims identified by the Examiner as "generic" are done only to identify claims which list multiple species. Thus claims 32, 39, 46, and 53 were identified as containing Markush groups for the purpose of Examination.

6. Claims **38-58** are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Response filed 15 September 2003.

7. The requirement is still deemed proper and is therefore made FINAL.

Specification

8. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (pp. 9 line 3). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP §608.01.

9. The disclosure is objected to because of the following informalities: space between word and comma (pp. 22 line 2); missing space "WO93/12227" (pp. 24 line 29); missing space "),(" (pp. 39 line 10); trademark should be superscript without parentheses "sepharose(TM)" (pp. 41 line 12). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims **31-37** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

11. The claims are drawn very broadly to methods of treating and/or preventing an amyloid-related disease in a subject by *active* immunization with an antigenic amount of a peptide to elicit an immune response against said amyloid component of an amyloid deposit wherein said peptide comprises at least one unnatural amino acid. The language of said claims encompasses a genus with at least 36 known diseases, the related peptides and derivatives thereof.

12. The specification teaches that the administration of particular anti-Aβ antibodies is able to reduce β-amyloid levels within the brains of mice which are transgenic for PDAPP. These mice exhibit Alzheimer's type over production and build up of β-amyloid within the brain. However, as recognized in the art, these mice do not exhibit Down's Syndrome or other amyloidogenic diseases, see in particular Schenk *et al.* (1999) "Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse." Nature **400**:173-77 (**IDS#148**) and Games *et al.* (9 February 1995) "Alzheimer-type neuropathology in transgenic

mice overexpressing V717F β-amyloid precursor protein." Nature **373**(6514): 523-527 (**IDS#109**). Thus, the model system used in the instant Specification is not recognized as providing for teachings that are predictive of the results which would be expected for the full scope of the claims. For example, the art recognizes that such *in vivo* models are not readily correlated to the human *in vivo* case. In particular, the art teaches a lack of correlation of beneficial effects shown in the mouse model system in humans; see in particular Münch & Robinson (July 2002) "Potential neurotoxic inflammatory responses to Aβ vaccination in humans." J. Neural Transmission 109(7-8): 1081-87 (**IDS#359**).

13. The specification fails to provide any guidance for the successful treatment of all 36 known amyloid-related diseases (see Table 1 of the Specification), and since resolution of the various complications in regards to *active* immunization treatment regimes for amyloid-related diseases is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations of all the listed proteins claimed, as well as mutants, fragments, and peptides thereof which contain at least one unnatural amino acid, with known amyloid related proteins, signs, and symptoms to correlate with a result ranging form the alleviation of symptoms (treatment) to total prevention. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

14. Also, "Prevention" is understood in the art to mean a total protection from disease or injury. Thus, given the high level of required effect, a high level of evidence showing prevention is also required. While the specification demonstrates a level of protection using an Aβ fragment for *active* immunization in the PDAPP mice, total prevention was not achieved {see Goldsby *et al.* (2002) Kuby Immunology 4th Ed. Chapter 18 "Vaccines" (pp. 453).

15. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using any given peptide defined so far in that it contains at least one unnatural amino acid. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a multitude of peptides based solely on the performance of a single Aβ peptide as highly problematic (see MPEP §2164.01). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods, such a disclosure would not be considered enabling since the state of the treatment of amyloid-related diseases and *active* immunization as highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

16. The following references are cited herein to illustrate the state of the art of amyloid-related diseases and *active* immunization treatment regimes.

17. While the use of Aβ immunogenic fragments comprising Aβ is feasible for treating Alzheimer's disease, Spooner *et al.* (13 December 2002) "The generation and characterization of potentially therapeutic Aβ antibodies in mice: differences according to strain and immunization protocol." Vaccine **21**(3-4): 290-297 (**IDS#369**) teaches that the route of administration, the regiment of administration, and the genetic background of the mouse used affects the production of anti-Aβ antibodies in response to Aβ immunization (Table 1 and 2). It is also noted that although no deleterious effects were observed, this too could be dependent upon genetic factors of the animal receiving the immunization (pp. 296). Thus uncertainty is found by use of Aβ as an immungen in regards to possible autoimmune reactions, general deleterious side effects, and variability in the production of anti-Aβ antibodies.

18. Furthermore Su *et al.* (6 February 1999) "Intravascular infusions of soluble β-amyloid compromise the blood-brain barrier, activate CNS glial cells and induce peripheral hemorrhage." Brain Research **818**(1): 105-117 (**IDS#361**) teaches that rats receiving twice daily intravascular administrations of $A\beta_{1-40}$ suffered damage to their blood-brain-barrier and elevated inflammation responses in their brains evidenced by activated microglia (Figures 2-4; pp. 113). Thus absent concrete guidance on how to practice the instant invention involving administration of an immunogenic peptide comprising at least one unnatural amino acid the skilled artisan is confronted with an undue burden of experimentation. First the skilled artisan must manufacture the appropriate peptides, then test each one to determine which have the desirable immunological effect.

19. Regarding the breadth of the claims, Goldfarb and Brown (1995) "The Transmissible Spongiform Encephalopathies." Annu. Rev. Med. **46**: 57-66 (**IDS#388**) teaches that prion

disease also known as transmissible spongiform encephalopathies (TSEs) encompasses kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), and fatal familial insomnia (Abstract). All of these diseases share a common element of a prion protein however the diseases are caused by different mutations and various isoforms may or may not be infectious (Table 1 and Table 2). In addition, Kovács *et al.* (2002) "Mutations of the Prion Protein Gene." J. Neurol. **249**: 1567-1582 (**IDS#389**) teaches that different mutations of the prion protein gene are responsible for different diseases with differing ages of onset and severity (Tables 1 and 2; Figures 4 and 5). Thus the skilled artisan is confronted with an undue burden of experimentation and unpredictability on how each individual isoform and/or mutation will affect the immune system of a patient [see also Elan Press Releases (1 March 2001 and 18 January 2002) (**IDS#225&226**)].

20. Regarding derivatives and fragments of the 36 amyloidogenic proteins encompassed by the claims and antibodies directed against them, the skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with deletion, insertion or substitution/replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick & Fetrow (2000) "From genes to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39 (**IDS#337**). For example, Jobling & Holmes (1991) "Analysis of structure and function of the B Subunit of cholera toxin by the use of site-directed mutagenesis." Molecular Microbiology **5**(7): 1755-67 (**IDS#334**) teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological

recognition, binding and toxicity. The skilled artisan further recognizes that immunological responses may depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted. Thus, both biological function and immunological recognition are unpredictable properties which must be experimentally determined. Further it is noted, that for particularly small peptides, conjugation appears to be required for promoting an effective immune response.

21. Moreover on the nature of the invention, the claims as written include the limitation that the immunogenic amyloid fragment include at least one unnatural amino acid. The Specification does not include any examples where this has been practiced leaving the skilled artisan to experiment, through trial and error in the absence of concrete guidance to determine which position in each of the 36 amyloid proteins can be substituted with any or all of the 34 unnatural amino acids to practice the invention as claimed {see Sipe (1992) "Amyloidosis" Annu. Rev. Biochem. **61**: 947-975 **(IDS#368)**}.

22. Regarding modification of β-amyloid as claimed, the problem of predicting protein structure in the absence of specific data (guidance) and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity, especially

if to be used to stimulate an immune response. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere suggestion of mutating, truncating, inserting, substituting residues into or breaking the β-amyloid into "fragments" and "peptides" to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), the nature and extent of changes that can be made in these positions while remaining useful for making therapeutic immune response. Although the specification cites art-recognized procedures for producing and screening for active muteins that produce a therapeutic immune response, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity and epitopes. This is of particular relevance when making antibodies or stimulating a desired immune cell response, especially those required in practicing a therapy. The art recognizes that function cannot be predicted from suggestion alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome

Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2 (**IDS#337**); Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen thusly generated peptides for their suitability in producing an immune response, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide an immune response with the necessary activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function as well as the resultant immune response elicited from these mutants, fragments, and peptides, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed method thereof in its full scope.

23. For instance, Fonseca *et al.* (June 1999) "The Presence of Isoaspartic Acid in β-Amyloid Plaques Indicates Plaque Age." Experimental Neurology **157**(2): 277-288 teaches that antibodies raised against Aβ containing isoaspartic acid (an unnatural amino acid) at position 7 will only bind the isoaspartic acid containing Aβ and not the wild-type Aβ (Figure 1). Also the anti-

isoaspartic acid Aβ antibody would only stain (bind to) isoaspartic acid Aβ containing plaques and not wild-type Aβ plaques (Figures 2-5). Thus the skilled artisan is presented with an example where an antibody raised against a peptide containing an unnatural amino acid will only bind proteins containing that same unnatural amino acid and not the wild-type isoform. Thus it is not predictable whether the antibodies and immune cells activated by the unnatural amino acid containing peptides will act to trigger said immune response against amyloid proteins absent any unnatural amino acids.

24. Concerning the level of predictability in the art, Diomede *et al.* (1996) "Activation effects of a prion protein fragment [PrP-(106-126)] on human leucocytes." Biochem. J. **320**: 563-570 (**IDS#390**) teaches that a fragment of PrP, residues 106-126 is toxic to neurons and astrocytes *in vitro* but stimulates neutrophils, monocytes, and lymphocytes, also *in vitro* (Figure 6). Thus PrP may be toxic to some cells but not to others. Also, Diomede *et al.* noted that immune cells may be able to survive the toxic effects of PrP because they are constantly dividing thus allowing for their numbers to be replenished following exposure to PrP (pp. 569). Thus the skilled artisan is confronted with an unpredictability of the effects of prion precursor protein and its fragments on cells.

25. Regarding the ancillary effects of the introduction of an immune response in a mammalian nervous system, the specification must establish that the antigens injection into the subjects produce a specific immune response and do not act as pyrogens (leading to cranial swelling for example). Goldsby *et al.* (2002) Kuby Immunology 4th Ed. Chapter 18 "Vaccines" (pp. 449-465) teaches that a large quantity of experimentation necessary to evaluate all the effects of the difficulty of predicating an immune response in the nervous system. This is due to

the fact that the stimulation of an immune response by an antigenic peptide does not mean that the patient has acquired protective immunity, in the case of the instant invention, the prevention of the development of an amyloid-related disease. An additional factor in "prevention" and active immunization is the successful development of immunological memory, not always a guarantee, requiring additional experimentation. Goldsby *et al.* also teaches that peptides are not as immunogenic as proteins and it is difficult for them to elicit both humoral and cellular immunity (pp. 461).

26. Moreover on the nature of an immune response required to fulfill the goal of the preamble, Singh (1997) "Neuroautoimmunity: Pathologic Implications for Alzheimer's Disease." Gerontology **43**:79-94 teaches that inflammation may play a key role in the Alzheimer's disease pathology (pp. 86). However, the Specification does not present sufficient direction/guidance about collateral damage due to a vigorous immune response in an immunological privileged area (such as the nervous system). The Specification as filed has only demonstrated a single successful antigenic presentation of a neurological protein (AN1792, a fragment of $A\beta_{42}$) which does not contain an unnatural amino acid, the complex nature of the invention, the unpredictability of the effects of antigens on the mammalian nervous system, and the breadth of the claims which fail to recite limitations for what constitutes a successful, controlled immune response in the mammalian brain, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope [see Elan Press Releases (1 March 2001 and 18 January 2002) (**IDS#225&226**)].

27. In addition, the percentage of D-amino acid containing components in amyloid plaques increases with age in Alzheimer's patients [Yang *et al.* (1997) "Effects of Racemization on the

Aggregational properties of the Amyloid β-Peptide in Alzheimer's Disease." Abstract—American Chemical Society 214th ACS National Meeting]. The role of these D-amino acids is not clear and so it is not clear what role, if any, D-amino acids may play in the pathogenesis of Alzheimer's Disease. Velazquez *et al.* (January 1997) "Aspartate residue 7 in amyloid β-protein is critical for classical complement pathway activation: Implications for Alzheimer's disease pathogenesis." Nature Medicine **3**(1): 77-79 teaches that a single substitution at position 7 in $A\beta_{1-42}$ of isoaspartic acid (an unnatural amino acid) for aspartic acid obliterated $A\beta_{1-42}$'s ability to activate the complement cascade, an essential component of cellular mediated immunity (Figure 1, Table 1). Thus the immunological significance and/or activity of each of the 34 possible unnatural amino acids must be assessed by the skilled artisan via extensive experimentation to evaluate the activity of each one for all 36 known amyloid proteins to practice the invention to the full scope as claimed.

28. The quantity of experimentation needed to make or use the invention based on the content of the disclosure, Castillo *et al.* (1995) "Amylin/Islet Amyloid Polypeptide: Biochemistry, Physiology, Patho-Physiology." Diabete et Metbolisme **21**: 3-25 teaches that amylin, the causative agent in islet amyloid formation in diabetes, is a 37 residue protein with a variety of actions in humans. The instant claims read on modifying/replacing one to all of the 37 positions in the amylin protein with one or any of 34 unnatural amino acids. Then injecting said modified proteins into patients to determine which, if any, have the desired effect of inducing a cellular (cell-based) or humoral (antibody-based) immune response as a therapy for islet amyloidosis. This constitutes an invitation to experiment with potentially 2.08×10^{53} potential

"immunogenic peptides" derived from a single amyloid protein (when only counting full-length wild-type and derivative amylin proteins).

29. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from treatment and risk assessment of Alzheimer's disease to other amyloidogenic disease as exemplified in the references herein.

Summary

30. Claims **31-37** are hereby rejected.

31. The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:

a. US 6,303,567 B1 (16 October 2003) Findeis *et al.*

b. US 5,985,242 (16 November 1999) Findeis *et al.*

c. US 2003/0166558 A1 (4 September 2003) Frangione *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

CJN
December 18, 2003